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# A glance on recent progresses in diagnosis and treatment of primary immunodeficiencies

## Progrese recente în diagnosticul și tratamentul imunodeficiențelor primare

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### Abstract

*Primary immunodeficiencies (PIDs)\* belong to the group of rare diseases which need more awareness by the relevant medical disciplines. Below a review on recent progresses in diagnosis and treatment of PIDs is given. Reducing the regrettable delay in diagnosis of PIDs (worldwide) is possible only when awareness is increased by doctors who may encounter patients with PID. This review shall serve this purpose. Progresses in understanding what the link might be between one genetic defect presenting in various phenotypes or how various gene defects may manifest by very similar PID phenotypes helps building awareness. Knowledge of PID favours early diagnosis, a cornerstone of optimal, sometimes life-long care at justifiable costs. The complexity of PIDs calls for clinical laboratory and clinical diagnostic performed by experts only. Exciting laboratory diagnostic progresses in early diagnosis of the most severe forms of PID are reviewed below. Progresses in curative therapies for PIDs, such as hematopoietic stem cell transplantation and gene therapies, are mentioned in short. About 80% of PID patients suffer from an antibody deficiency syndrome and can profit from non-curative replacement therapies with human immunoglobulin G concentrates. Modes of application, safety and hints for dosing of replacement therapies to reduce frequencies of severe infections are mentioned below. Thanks to the increasing quality of care, patients survive adolescence. A glance is given on the problems of transition to the adult medicine setting.*

*\*for abbreviations please consult the list of abbreviations at the end of the manuscript*

**Keywords:** Awareness, early diagnosis, gene therapy, hematopoietic stem cell transplantation, immunoglobulin G concentrates, new-born screening, primary immunodeficiencies, replacement therapy

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## Progress in understanding the pathophysiology of primary immunodeficiency diseases

Primary immunodeficiencies (PIDs)\*, in their majority, relate to an impaired capacity of patient's immune system to fight infections, recurrent ones or infections with a very narrow range of pathogens (1). Some forms, when untreated, result in death early in life; others, in chronic debilitating infections and tissue remodelling. In addition, genetic defects identified more recently may result in an autoimmune-inflammatory phenotype of PID. Over 200 different genetic defects leading to PIDs have been described so far. With the progress of knowledge, the classification of PIDs has been updated regularly. However, the most forefront classification also has become an issue of debates because for the everyday clinical work such classification has become a topic able to be overlooked by much specialised clinicians and researchers only (2-4).

Patients with recurrent, severe or unusual infections steadily are fuelling clinical research, thereby continuously increasing the number of genetic defects underlying PIDs (5;6). Understanding the pathogenesis of PID is essential for optimal therapy of PID patients and cost effectiveness of care. National and international registries are excellent sources for important information. Due to the increasing numbers of patients included to the various registries, more and more precise statements can be made on how an early, optimal and effective treatment of PID patients might become possible.

Definitions of rare disease in the EU and in the USA are: an incidence of  $\leq 1/2000$  (EU) or  $\leq 200,000$  patients (USA). PIDs are rare diseases with a prevalence of 5-6 patients per 100,000 inhabitants in France (highest report in the EU) (7). A higher prevalence has been reported from countries with consanguine marriages (8). CVID

is the most common phenotype of PIDs and embraces a heterogeneous group of patients which either suffer from infections only or in addition from inflammation, granuloma, autoimmunity, colitis, cytopenia and malignancy (9-12). Ten to twenty percent of the CVID phenotype have a familial trait and in about 3% of CVID 10 different gene defects or polymorphisms have been identified in the last 10 years (deficiencies of BAFF-R, CD19, CD20, CD21, CD81, ICOS, LRBA, MSH5, NF- $\kappa$ B2, PI3K $\delta$ , and TACI) (13;14). In addition to CVID, haematological malignancies, autoimmune-like, inflammatory, and malignant conditions are comorbidities of many other PID phenotypes (15).

Beside the classical PIDs, the non-classical PIDs are Mendelian conditions which are characterized by a very narrow spectrum of opportunistic infections – sometimes limited to one microbial genus or species – while presenting a normal development of the principal leukocyte subsets. These non-classical PIDs comprise susceptibility to mycobacteria (10 genetic defects identified so far), predisposition to neisserial infections (e.g. complement deficiencies) and invasive bacterial disease, predisposition to invasive fungal infections and chronic mucocutaneous candidiasis, predisposition to HPV infection, HSV encephalitis and EBV infection.

The recognition and diagnosis of PID form beside of a clinician's observation of an individual clinical and/or immunological phenotype remains difficult. Therefore, attempts to provide guidelines for clinicians at the bedside were published recently (16).

## PID diagnosis - As early as possible

Shortening the delay in diagnosis of PID is the key for cost-effective therapies and is helping to keep health care costs reasonable without restricting patients' access to the relevant therapies (17;18). The platform for early diagnosis is

medical awareness. To increase awareness in all medical disciplines that may encounter patients with PID and the wide spreading of the ‘warning signs of primary immunodeficiency’ can be an effective tool (19;20). However, it has to be stressed that for taking the correct actions the widely promulgated “warning signs” have to be interpreted by experts (21). Other tools to raise awareness might be medical discipline-specific reviews (22-26) or data mining in national or international registries. National registries may not have the power of international registries (<http://esid.org/Working-Parties/Registry/ESID-Online-Registry>, accessed April 2014).

Hints for PID need a follow-up by standard diagnostic measures, e.g. serum immunoglobulin isotype levels plus specific response to vaccination, small lymphocyte panel plus B cell panel plus CD45RA CD4 T cells (+ T cell proliferation) (27). If the results are not conclusive, the next level might include specific membrane protein detection by flow cytometry (28-30). Established diagnostic criteria for SCID variants and recently published guideline for new-born screening are available (31;32).

Combined immunodeficiencies (CIDs) need to be recognized and separated from CVID. CIDs are T-cell impairments and can manifest as infections by intra/extracellular “opportunistic agents”. Even though sharing common clinical features, the discovery of new causative gene alterations led to the identification of novel complex clinical phenotypes of CID, with manifestations of autoimmunity/inflammation, allergy and lymphoma. CIDs represent about 20% of PIDs with approximately 80 different gene alterations (prevalence according to the French registry 1.1/100,000 or ~1/20,000 births). The detection of these alterations relies on nucleic acid sequencing methods and can prevent the death of affected children.

Population-based new-born screening (NBS) is a promising technique to detect from Guth-

rie cards severe combined immunodeficiency (SCID) or combined immunodeficiency (CID) based on the T-cell receptor (rearrangement) excision circles (TREC) assay (33). At present, the cut-off of the test is a problem because a wide spectrum of detected non-SCID disorders with T-cell lymphopenia. Although an evaluation of the population based SCID-NBS outside the US has started, and despite the proof of cost effectiveness of SCID-NBS, issues such as costs, ethics, moral, social, legal and policy remain the main barrier against wide implementation in countries other than the USA. Performing the TREC assay only might miss some forms of severe PIDs (34).

The potency of the population-based NBS for PIDs can be enhanced by introduction of the  $\kappa$ -deleting recombination excision circles (KREC) assay which allows for additional detection of B cell lymphopenia (35;36). The combination of both tests considerably expands the diagnostic range at a cost increase of about 0.10 Euro only. Furthermore, information from of TREC and KREC levels can also be used as a surrogate marker of lymphocyte output in acquired immunodeficiencies and it also might allow to follow therapy success (37). Laboratory methods for population-based dried spot analyses are expanding rapidly. Extension of the mass screening for PIDs not detectable by TREC and KREC assay might come at low cost from dried blood sample analysis by mass spectrometry (38)

The clinical and immunologic heterogeneity of CVID remains a diagnostic challenge (39;40). Recently a heterogeneous group of patients was classified according to B cell phenotype, KREC analysis, and SHM pattern. Five B-cell patterns were identified each reflecting an immunologically homogenous patient group with proposed unique pathophysiology. Another diagnostic challenge is the differential diagnosis between particular forms of CVID and CID. Time will

show whether the TREC, KREC assay or genome wide array analyses might be helpful in understanding clinical heterogeneity of CVID and dissect it from CID (14;41).

In 2006 the generation of “induced pluripotent stem cells” (iPSC) was reported for the first time by epigenetically reprogramming of somatic cells through the exogenous expression of transcription factors. The technique then could be adapted to human fibroblasts (42;43). Induced pluripotent stem cells (iPSCs) offer a unique potential for understanding the molecular basis of diseases and disease development. The study of primary immunodeficiencies (PIDs) has largely been based on animal models, in-vitro assays, and was suffering from the limited access to disease-specific tissue. Application of this technique one day might become an additional tool for functional investigation of human PIDs and other disorders as well as it might provide new medicines (44).

### **Optimizing replacement therapies at high safety levels**

Immunoglobulin replacement therapies are the therapy of choice for the majority (~80%) of PID patients. Replacement therapy is not curative but can ensure over long-term acceptable Quality of Life. Depending on the country, there is a more or less broad offer of various immunoglobulin concentrates available (<http://www.ip-opi.org/index.php?page=immunoglobulin-companies>; accessed May 2014).

Treatment of PID, as any other rare disease, requires expertise. A recent study in the northern hemisphere compared management of patients dependent on replacement therapies. US physicians with >10% of their practice devoted to primary immunodeficiency managed PID therapy very similarly to their colleagues in EU, while in US physicians whose clinical practice was composed of <10% of PID patients management pro-

ocols differed from the other two groups (45). Low percentage of PID patients treated in clinic or practice may not optimally comply with patients' need.

According to the American Academy of Allergy, Asthma and Immunology (AAAAI), replacement therapy is definitively beneficial for PIDs with absent B cells and PIDs with hypogammaglobulinaemia and impaired specific antibody production; it is probably beneficial for PIDs with normogammaglobulinaemia and impaired specific antibody production; and unlikely to be beneficial for isolated IgA and IgG4 deficiency (46). According to the EU PID Consensus Conference outcomes, the indication for replacement therapy is given for all patients with IgG of < 2g/L - with the exception of children without severe infectious complications (physiological hypogammaglobulinaemia of childhood); at levels of 2-5 g/L when associated with recurrent infections; and with IgG of > 5g/L when there is a deficiency in the formation of antibodies to specific antigens and serious or recurrent infections ([http://ec.europa.eu/health/ph\\_projects/2005/action1/docs/action1\\_2005\\_exs\\_01\\_en.pdf](http://ec.europa.eu/health/ph_projects/2005/action1/docs/action1_2005_exs_01_en.pdf); accessed April 2014).

In an environment of ever increasing use of immunoglobulin concentrates it has to be ascertained that PID patients have now and in future a continuous and sufficient access to this plasma derived medicinal product (47). Treatment based on evidence based practice guidelines (48;49) and Prioritisations Plans, of which the most have been compiled into a European consensus proposal (50), are valuable tools for an appropriate use and the best prioritisation of Ig concentrates in and outside the PID field. These documents can be adapted e.g. to the needs of Romanian patients and care givers.

The proportion of patients receiving SCIG is continuously increasing: new products, less frequent adverse events, sustainably higher immunoglobulin levels in the circulation and the

option of easy to perform home therapy thereby possibly reducing costs, at least in certain countries, support this development (51-54). SCIG can be applied with the help of a pump e.g. every two to three days, weekly, and three weekly to monthly facilitated by hyaluronidase or daily by "rapid push" (55-57). Availability of IVIG and SCIG allows for adapting replacement therapy to the clinical situation and the preference of the treating physician and/or how it is best suitable for the patient's individual needs (58). However, SCIG should be applied with care when risk factors exist (e.g. severe thrombocytopenia, bleeding disorders or anticoagulation therapy).

Dosing levels in replacement therapy are an eternally discussed topic. As a rule it is accepted that increasing the dose reduces risk for severe infections and this is true for the i.v. and the s.c. route of application of immunoglobulins (59;60). In a naïve patient, or a patient not having received replacement therapy for more than 3 months, the aim is to increase circulating IgG rapidly and this is achieved best by initially slow infusion via the i.v. route with doses starting at 0.4-0.6 g/kg b.w./3-4 weeks. Furthermore, evidence-based medicine data indicate as a rule that trough levels above 5-6 g IgG/L being "effective". However, there are patients who are not able to cope with these rules. Parameters identified so far for not being able to cope with the rules are (i) patient's residual levels of IgA, (ii) serum concentration of mannose-binding lectin, (iii) the polymorphism of the neonatal FcRn receptor, and (iv) B cell defects (61-65). In some patients the optimisation of replacement therapy might require measurement of e.g. anti-pneumococcal antibodies. An optimal maintenance therapy of PID patients is "individualized" and does not follow trough levels and is not weight based, i.e. a biological level should be achieved and this level might need adaptation in winter-versus summer-time (66).

When shifting from IVIG to SCIG difference exist what US and European authorities consider as adequate (67;68). In daily practice and in general, mean actual levels of circulating IgG in patients has risen over the decades, and due to several factors tend to be higher when on SCIG. Furthermore, steadily increasing mean levels of IgG in the circulation of PID patients are driven by deeper insight into pathophysiology. Particularly autoimmune and inflammatory conditions associated with antibody deficiency syndromes may support orientation towards treatment doses corresponding to those applied for immunomodulation. Some caution is advised when discussing trough levels. Because of the difference in application intervals and doses, pharmacokinetics differs and trough levels might not be directly comparable.

#### ***Therapy of antibody deficiency syndromes-associated non-infectious complication***

Beside recurrent respiratory and gastroenteric infections, autoimmune-like, inflammatory and malignant conditions in a part of PID patients are associated with increased mortality and pose major clinical challenges. The background for these complications remains unknown. For CVID differences in peripheral T- and B-cell compartments of patients might have some influence, i.e. disease-related complications appear to be more frequent in patients with naïve CD4<sup>+</sup> T-cell defects (69). Optimal treatment of disease-related complication in CVID remains an unmet medical need (9;70). Treatment needs expertise to take the decision for watchful waiting vs active therapy if available at all. Some therapy options might be optimal IgG substitution, supportive therapy (parenteral nutrition), antibiotics, corticosteroids / Budesonide, immunosuppressive therapy (Methotrexate, Azathioprine, biosimilars (Rituximab, Infliximab), and transplantation. It remains unclear how far the com-

plications are infection-related/triggered. Multi-centre (observational) studies and data mining in registries are required to obtain answers on how best to treat these conditions.

#### ***Transition of PID patients to the clinic for adults***

Transition, i.e. the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centred to adult-oriented health care systems, is a long-haul interdisciplinary project and remains an unresolved problem (71). Particular centres for PID/rare diseases might be best suited in supporting patients on their sometimes difficult journey into adulthood by e.g. establishing a “transition clinic”. After the transition phase or PIDs with late onset diseases/late diagnosed disease, patients might be confronted with difficulties to access specialists and obtain optimal therapy. Very recently, a scoring system was presented how to establish replacement therapy in adult PID (72).

#### ***Pathogen safety of replacement therapy***

Measures requested by authorities such as current Good Manufacturing Practice (cGMP) and voluntary quality standards implemented by the plasma fractioning industry have pushed pathogen safety of immunoglobulin concentrates high and this is indicated by no reports of transmission of emerging viruses (SARS CoV, West Nile Virus and others), zoonotic pathogens or the agent of variant Creutzfeldt-Jacob disease in the last decade (73;74).

#### ***Adverse events related to replacement therapy***

Adverse events to IVIG and less frequently to SCIG in their majority are mild to moderate in intensity and largely self-limiting. Adverse events to therapeutic immunoglobulin concentrates might be related to the active component

IgG, to impurities or to excipients in the preparations. The active component-related adverse events are inherent to replacement therapy. Inherence in part is due to the nature of our immune system, which on one hand serves host defence and on the other hand it also is part of the peripheral immunologic homeostasis network and serves removal of altered and senescent self. IgG concentrates derive from the immune system of several thousand healthy donors. Their application in patients results in the desired recognition and subsequent removal of possible pathogens but inevitably also results in the recognition of the recipient's variable-region connected immune network (75) and the recognition of altered or senescent tissue in an alloimmune fashion (76). This type of adverse events, as a consequence, is more patient than product dependent. Frequency of adverse events after IVIG infusion usually can be kept low by low infusion rates and avoiding some excipients in IVIGs (77). Severe adverse events are acute renal failure mainly due to osmotic nephrosis (predominantly by excipient), anaphylaxis, i.e. interaction of co-fractionated IgA in the product (impurity) with anti-IgA very rarely present in the plasma of the patient, aseptic meningitis, haemolysis i.e. due to anti-blood group antibodies (impurity), TEEs i.e. due to FXIa (impurity) and transfusion-related acute lung injury (78). Reports on increasing numbers of haemolysis and TEEs with severe consequences are a recent focus of concern. Both types of AEs are strongly related to the dose applied. TEEs have been found to be associated with elevated levels of activated coagulation factor XI (FXIa) and kallikrein (79) and resulted in the batch-wise testing and removal of FXIa ([http://www.web-medcentral.com/article\\_view/2002](http://www.web-medcentral.com/article_view/2002); accessed April 2014). Despite all measures, patient- and administration-related factors for TEE remain; risk factors are age, underlying disease, co-morbidities, high protein doses and rapid infusion.

Haemolysis is a long recognized complication of IVIG therapy occurring at an apparent frequency of <1/100,000 patients treated and has been observed with intramuscular, subcutaneous and predominantly with intravenous preparations. In the last decade an increase in haemolysis rates were observed when infusing certain IVIG brands at immunomodulatory doses (80) while in a review of IVIG replacement trials an increase in direct Coombs test was observed without evidence of haemolysis (81) (for the courtesy of the reader: Gammagard liquid (US) corresponds to KOIVIG (EU)). Haemolysis can manifest as haemolytic anaemia or in isolated cases as haemolysis-related renal dysfunction/renal failure or disseminated intravascular coagulation and death. Isoagglutinins, e.g. A, B and AB have been attributed to mediate these higher frequencies (82) although release criteria of US & EU products include specifications for anti-A & anti-B antibodies of  $\leq 1:64$  in the direct haemagglutinin assay. As IVIG-associated haemolysis occurs although products meet licensed specifications risk factors other than isoagglutinins are supposed, e.g. inflammatory conditions and rapid infusion. Meanwhile the plasma fractionating industry has taken measures to reduce isoagglutinin levels in immunoglobulin concentrates, e.g. by withholding from pooling high-titre donations and/or by introducing a polishing step which reduces isoagglutinins by immunoaffinity chromatography.

## Vaccination and PID

Vaccination can be an excellent diagnostic tool in PID. Otherwise, PID vaccination cannot have a universal role because the difference in the various forms of PIDs. In patients with low antibody production vaccination might be considered in order to minimize the recurrence of episodes of infection using killed pathogens or subunits (refrain from the vaccination with (at-

tenuated) live vaccines!). There are only very few controlled studies reported with most data generated in children. The grade of treatment recommendation drawn from these studies remains C (possible effective; 2<sup>nd</sup> or 3<sup>rd</sup> line treatment) and in rare cases it might reach recommendation grade B (possibly effective, use as alternative to other therapy options). After having consulted a PID specialist, vaccination may be performed ([www.cipo.ca/Vaccines.doc](http://www.cipo.ca/Vaccines.doc); accessed June 2014). Thus, dead influenza vaccine is safe, can be applied for seasonal prophylaxis but may not work well in patients with CVID while patients with IgA deficiency might profit from it. However, clinical improvement might be observed even in absence of detectable increase of protective antibody levels and this has resulted in best practice statement from the UK ([http://www.rcpch.ac.uk/sites/default/files/asset\\_library/Publications/I/Immunocomp.pdf](http://www.rcpch.ac.uk/sites/default/files/asset_library/Publications/I/Immunocomp.pdf); accessed June 2014) and uncertainties together with the growing neglect of societal adherence to routine immunizations has prompted the Medical Advisory Committee of the Immune Deficiency Foundation (US) to issue recommendations based on published literature and the collective experience of the committee members (83). The prophylactic vaccination of household members of these patients groups is highly recommended.

## Curative therapies for PID

### *Haematopoietic stem cell transplantation / bone marrow transplantation*

Between 1968 and 2012 more than 2250 transplantations for SCID and more than 5000 for non-SCID PIDs have been performed (84). The methods applied are bone marrow transplantation, cord blood transplantation and machinery supported collection of HSCs. Very early transplantation (indicated by family history or population-based NBS) significantly improves out-

come irrespective of donor choice, conditioning regimen used, and underlying genetic diagnosis. Other factors of steadily and incrementally improving HSCT outcome encompass reduced intensity condition regiment, increasing expertise in ablation of certain donor cell populations in order to provide a balance between engraftment and graft-versus-host disease (GvHD), low dose serotherapy new drugs allowing reduction of veno-occlusive disease, close viral and fungal surveillance, and more sophisticated supportive care (85-87). Very recent US NBS data indicate that a prolonged time window for transplantation might be gained when timely TREC-NBS prompt immediate measures to avoid infections and organ damage. Transplantation in some CID can pose a considerable challenge as infection, autoimmunity/inflammation, allergy and lymphoma have to be taken into account.

Post HSCT viral infections are (severe) complications and also pose a major therapeutic challenge. Emerging therapies are Rituximab for EBV and CMX010 for CMV infections.

#### ***Patient-derived induced pluripotent stem cells***

The iPSC technique allows the access to previously inaccessible diseased tissue and in turn allows the development of novel treatment strategies such as has been reported for X-linked CGD (88).

#### ***Gene therapy***

Gene therapies are curative measures for PIDs (89-91). They belong to the emerging group of “personalised” therapies. Site-specific insertion and the development of safe and effective self-inactivating viral vectors have reduced the risk for post-transplant malignancies (insertional oncogenesis). The process involves the isolation of autologous haematopoietic stem cells (HSC), ex vivo introduction of the gene of interest by viral vector, expansion of cells and

‘transplantation’ of the gene-corrected HSC (92). The recent vectors are retroviruses, SIN retroviruses and lentiviruses engineered to have no potency for insertional oncogenesis (91;93). PID conditions treated so far or being in clinical studies are SCIDX1, ADA-SCID, CGD, and WAS. For the future all PID patients identified with genetic defects are potential candidates for gene therapy (94). This includes those 10 gene defects with the ‘CVID’ phenotype which have been identified in the last 10 years (see above). Attempts for scientific assessment for marketing authorization of ‘advanced therapy medicinal products’, e.g. of viral vectors based gene therapies, have been initiated ([http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000126.jsp&mid=WC-0b01ac05800292a5](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000126.jsp&mid=WC-0b01ac05800292a5); [http://ec.europa.eu/health/human-use/advanced-therapies/developments/index\\_en.htm](http://ec.europa.eu/health/human-use/advanced-therapies/developments/index_en.htm); <http://www.genetherapy.net.com/europe.html>; all accessed June 2014).

### **Conclusions**

Developments in understanding pathogenesis, diagnosis and therapy of PIDs have progressed rapidly in the recent years. Particular note has to be given to the new screening techniques allowing diagnosis at a time point where no organ damage has occurred yet. Nevertheless, some problems remain such as the low awareness for PID or the emergence of complex ethical problems due to the new diagnostic tools. I hope this short review helps raising awareness for a rare disease where for a large part of the patients satisfying therapy options exist.

### **List of abbreviations**

BAFF-R: B cell activating factor receptor (of the tumour necrosis factor family); tumour necrosis factor receptor superfamily member 13C; TNFRSF13C

BMT: bone marrow transplantation



CD: cluster of differentiation  
 CID: combined immunodeficiency  
 cGMP: current good manufacturing practice  
 CMV: cytomegalovirus  
 CVID: common variable immunodeficiency  
 EBV: Epstein-Barr virus  
 ESID: European Society for Immunodeficiencies  
 FcRn: Fc receptor of the newborn; Brambell receptor  
 GvHD: graft-versus-host disease  
 HPV: human papilloma virus  
 HSCT: hematopoietic stem-cell transplantation  
 HSV: herpes simplex virus  
 ICOS: inducible (T-cell) co-stimulator  
 iPSC: induced pluripotent stem cells  
 IVIG: human immunoglobulin G concentrate applicable via the intravenous route  
 KREC:  $\kappa$ -deleting recombination excision circle  
 LRBA: lipopolysaccharide-responsive and beige-like anchor protein  
 MSH5: human homolog of Escherichia coli MutS 5  
 NBS: new-born screening  
 NF- $\kappa$ B: nuclear factor kappa-light-chain-enhancer of activated B cells  
 PI3K $\delta$ : phosphatidylinositol-3-OH kinase PI(3)K catalytic subunit delta  
 PID: primary immunodeficiency  
 PID: primary immunodeficiency disease  
 SARS-CoV: severe acute respiratory syndrome corona virus  
 SCID: severe combined immunodeficiency  
 SCIG: human immunoglobulin G concentrate applied via the subcutaneous route  
 SHM: somatic hyper mutation  
 SIN: self-inactivating  
 TACI: transmembrane activator and calcium modulator cyclophilin ligand interactor; tumor necrosis factor receptor superfamily member 13B; TNFRSF13B;  
 TEE: thromboembolic event  
 TREC: T-cell receptor (rearrangement) excision circle

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